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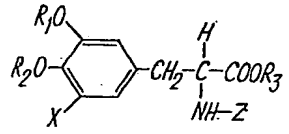
(54) BETA-PHENYLALANINE DERIVATIVES

(71) We, RECHERCHE ET INDUSTRIE THERAPEUTIQUES R.I.T., a body corporate organized under the laws of Belgium, of 13, rue du Tilleul, Genval, Belgium, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention relates to new beta-phenylalanine derivatives and to the preparation thereof.

The new beta-phenylalanine derivatives of this invention may be represented by the following general formula I.



FORMULA I

wherein:

R_1 and R_2 are identical or different and represent methyl or ethyl, one of them being also possibly hydrogen or a carboxylic acyl radical of from 2 to 30 carbon atoms, but preferably R_1 and R_2 are different, one of them representing hydrogen, the other representing methyl,

R_3 represents hydrogen, a pharmaceutically acceptable non-toxic alkali metal, ammonium, a pharmaceutically acceptable non-toxic protonated amine with which the rest of the molecule forms an acid addition salt, an alkyl radical containing from 1 to 30 carbon atoms or an alkenyl radical containing from 2 to 30 carbon atoms, said alkyl or said alkenyl radicals having a straight or a branched chain, but preferably R_3 represents hydrogen,

X represents chloro, bromo, iodo or fluoro and preferably chloro or bromo, and

Z represents hydrogen or a carboxylic acyl radical containing from 2 to 30 carbon atoms, but is preferably hydrogen.

The compounds of general formula I exhibit prolonged hypotensive activity and are therefore useful in lowering blood pressure. Preferred compounds such as 3-methoxy-4-hydroxy-5-chloro-β-phenylalanine (hydrochloride), 3-methoxy-4-hydroxy-5-bromo-β-phenylalanine (hydrochloride) and 3-hydroxy-4-methoxy-5-bromo-β-phenylalanine (hydrochloride) have been found to lower blood pressure in hypertensive rats when administered by oral or subcutaneous route at doses of from 30 to 100 mg/kg in the procedure described by M. GEROLD, A. HURLIMANN and C. von PLANTA in Helv. Physiol. Acta *24*, 58 (1966).

[*Price 5s. 0d. (25p)*]

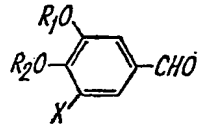
The compounds of formula I may be administered by the oral, intramuscular, intravenous or subcutaneous route.

The compounds of general formula I with a free amino group are preferably administered in the form of a non-toxic acid addition salt thereof, said acid being an inorganic acid, such as hydrochloric acid, hydrobromic acid, phosphoric acid or sulfuric acid. When R_3 is alkyl, other possible acid addition salts are those with organic acids such as acetic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, palmitic acid, methanesulfonic acid or ethanesulfonic acid, said addition salts being also within the scope of this invention.

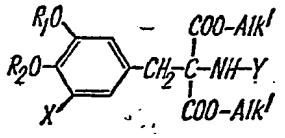
These novel beta-phenylalanine derivatives can be compounded and formulated accordingly into pharmaceutical preparations for oral or parenteral administration with pharmaceutically acceptable diluents or carriers. The compositions may take the form of tablets, powders, granules, capsules, suspensions, solutions, emulsions and injectable solutions and suspensions. Such compositions are considered within the scope of this invention.

The present invention also relates to the preparation of the compounds of general formula I.

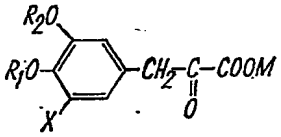
The compounds which are used for the preparation of the products of the present invention are substituted 5-halo-benzaldehydes, N-substituted aminomalonic acid lower alkyl (1—4 carbon atoms) ester derivatives and phenylpyruvic acid derivatives, which are represented respectively by the following general formulae II, III and IV



FORMULA II



FORMULA III



FORMULA IV

In these general formulae II, III and IV,
R_1, R_2 and X are as defined above,
Alk′ represents a lower alkyl radical with a straight or branched chain containing from 1 to 4 carbon atoms, preferably methyl or ethyl,
Y represents a formyl, acetyl, benzoyl, phthaloyl or benzyloxycarbonyl radical, and M represents hydrogen, a pharmaceutically acceptable non-toxic alkali metal, ammonium or a pharmaceutically acceptable non-toxic protonated amine with which the rest of the molecule forms an acid addition salt.

More particularly, the compounds of general formulae II, III and IV wherein R_1 is hydrogen and R_2 is methyl or ethyl will be represented hereafter by formulae IIb, IIIb and IVb, respectively.

The compounds of general formulae II, III and IV are valuable intermediate compounds for the synthesis of compounds of formula I, those of general formula II being also valuable intermediates in the synthesis of alcohols, acids, esters, quinoline derivatives and hydantoin derivatives, all congeners of known compounds of valuable interest in the pharmaceutical field.

According to the respective nature and position of R_1 and R_2, the intermediate

3,4-disubstituted-5-halobenzaldehydes of formula II and the N-substituted aminomalonic acid ester derivatives of general formula III may be obtained by different ways, some of which are hereafter described as illustrative under headings *A* to *C*.

A.

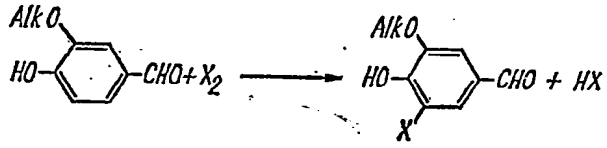
When R_1 is methyl or ethyl and R_2 is hydrogen, the intermediate N-substituted aminomalonic acid ester derivative is obtained from the corresponding 3,4-disubstituted benzaldehyde. The 3,4-disubstituted benzaldehyde is first halogenated to yield the corresponding 5-halobenzaldehyde, the reaction being preferably conducted at room temperature in a suitable solvent such as acetic acid. When X is fluoro, the 3,4-disubstituted 5-fluorobenzaldehyde is preferably prepared from the corresponding 5-bromobenzaldehyde by halogen transposition.

The obtained 5-halobenzaldehyde is then reduced in mild conditions to yield the corresponding alcohol, using, for instance, an alkali metal borohydride to avoid hydrogenolysis of the carbon-halogen bond.

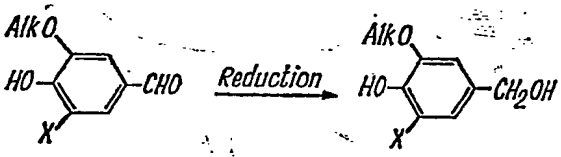
By reaction with a hydrohalic acid, for instance hydrochloric acid, in an anhydrous medium, the alcohol is transformed into the corresponding halo derivative. This derivative is allowed to react with an alkali (preferably sodium) di-lower (1 to 4 carbon atoms) alkyl N-substituted aminomalonate (preferably the di-methyl or di-ethyl ester) to yield the N-substituted aminomalonic acid ester derivative of formula IIIa. This step is carried out in a suitable solvent, preferably at the reflux temperature. Examples of suitable solvents are anhydrous ethanol, benzene, dimethylformamide and toluene.

This procedure is summarized in the following reaction scheme 1:

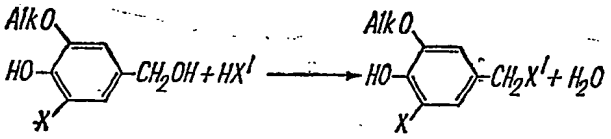
Scheme 1

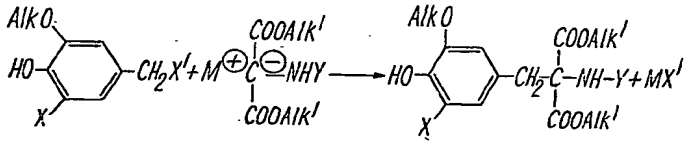


FORMULA IIa



FORMULA IIa





FORMULA IIIa

wherein

Alk represents methyl or ethyl,

Alk' represents a lower alkyl radical of from 1 to 4 carbon atoms, preferably methyl or ethyl,

X and X′ — which may be identical or different — represent halogen, X being preferably chloro or bromo and X′ being preferably chloro,
$M^{\oplus}$ represents an alkali metal ion, preferably a sodium ion and
Y is as defined above.

B.

When, in general formula I, R_1 represents hydrogen, and R_2 represents methyl or ethyl, the intermediate N-substituted aminomalonic acid ester derivative is obtained from a 3-alkoxy-substituted benzaldehyde, said alkoxy group containing from 1 to 4 carbon atoms.

The 3-alkoxy-substituted benzaldehyde is first halogenated to yield the corresponding 5-halo-benzaldehyde which is de-alkylated to yield the 5-halo-protocatechualdehyde, which is then selectively alkylated in position 4.

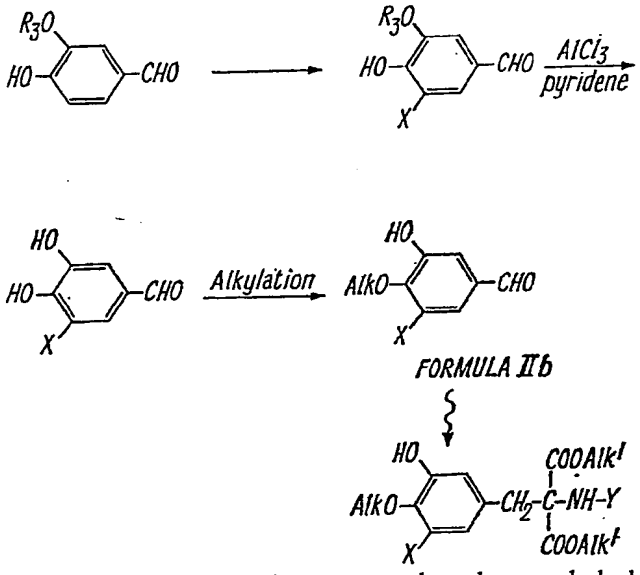
The said de-alkylation is carried out using any procedure known to the art for such a reaction, for instance with anhydrous aluminium chloride and pyridine in methylene chloride, under the influence of heat.

The O-alkylation which is selective for position 4 is carried out in an inert solvent using any alkylation procedure known to the art, provided that the molar ratio of alkylating agent to aldehyde is less than two. Acetone plus methyl iodide and dioxane plus diazomethane are examples of solvent/alkylating agent systems.

The 3-hydroxy-4-alkoxy-aldehyde is then successively reduced, reacted with hydrohalic acid and then reacted with the alkali metal di-lower alkyl N-substituted aminomalonate as described under heading A.

The following scheme 2 describes the particular features of this procedure.

Scheme 2

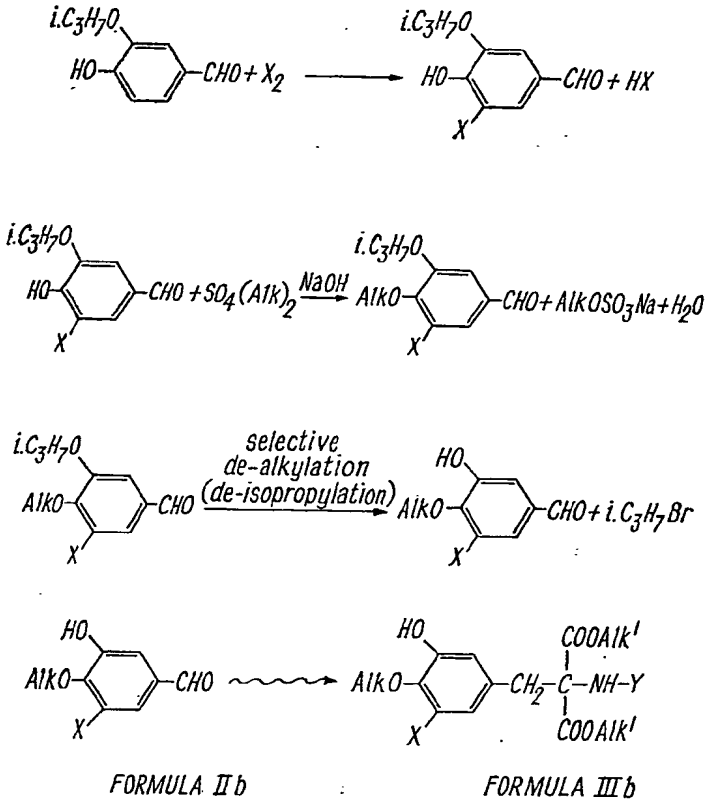


wherein R_3 is alkyl with 1—4 carbon atoms, the other symbols being as defined above.

Alternatively, the intermediate N-substituted aminomalonic acid ester derivative is also possibly obtained from a 3-alkoxy-substituted benzaldehyde wherein the alkoxy group contains more than two carbon atoms, e.g. 3-isopropoxy-4-hydroxybenzaldehyde. This starting material is first halogenated to yield the corresponding 5-halobenzaldehyde which is then alkylated, for instance by dimethyl- or diethylsulfate to yield the corresponding 3-isopropoxy-4-alkoxy-5-halo-benzaldehyde. This product is then de-isopropylated, for instance by refluxing for a very short time (from one to ten minutes) a solution thereof in aqueous hydrobromic acid (48%). The de-isopropylated compound is then successively reduced and reacted with a hydrohalic acid and then with the alkali metal di-lower alkyl N-substituted aminomalonate as described under heading A.

The following scheme 3 describes the particular features of this procedure.

Scheme 3



FORMULA II b FORMULA III b

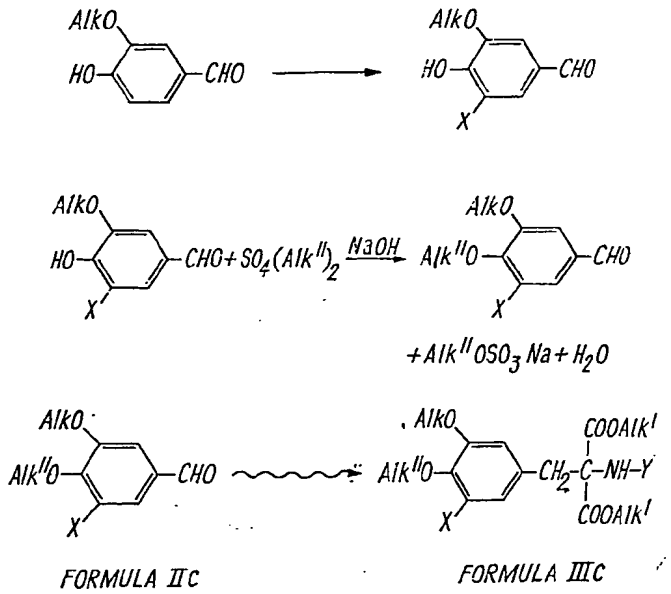
wherein the symbols are as defined above.

C.

When, in general formula I, both R_1 and R_2 represent methyl and/or ethyl, the intermediate N-substituted aminomalonic acid ester derivative is obtained according to the procedure described under heading A in scheme 1, the substituted 4-hydroxybenzaldehyde being transformed into the corresponding 4-alkoxy compound before reduction of the aldehydic group into the corresponding alcoholic group. This alkylation step may be performed by methyl- or ethyl-sulfate in aqueous sodium hydroxide.

The following scheme 4 describes the particular features of this procedure.

Scheme 4



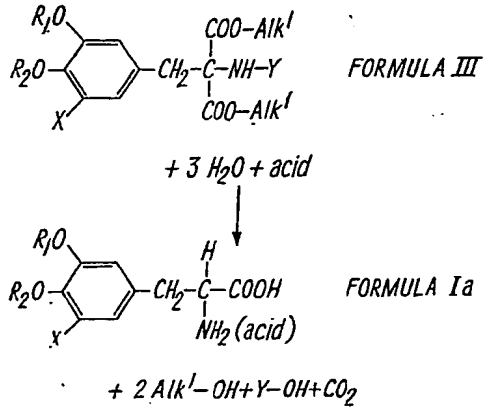
wherein
Alk and Alk'' are identical or different and represent methyl or ethyl, the other symbols being as defined above.

The compounds of general formula I are prepared from the compounds of general formula II, using various methods, among which preferred methods are those hereinafter described under heading Method I and Method II.

METHOD I

According to this procedure, the derivatives of general formula I wherein R_3 and Z are both hydrogen are prepared as described in scheme 5 shown hereinafter by hydrolysis and decarboxylation of appropriately substituted 2-benzyl-2-amino-malonic acid esters of general formula III. The reaction is conducted in a solvent under the influence of heat in acid medium and in the presence of a reducing agent. The amino acid thus obtained may be thereafter transformed into the desired salt, ester and/or acylated compound by procedures known to the art.

Scheme 5



In this scheme 5,
R_1, R_2 and X are as defined above,

Alk' represents a lower alkyl radical with a straight or branched chain of from 1 to 4 carbon atoms, preferably methyl or ethyl, and
Y represents a formyl, acetyl, benzoyl, phthaloyl or benzyloxycarbonyl radical.

To avoid dealkylation of the alkoxy substituents in the phenyl nucleus, the reaction is conducted in mild conditions which are characterized by a reaction period of between 9 to 10 at a temperature of between 95° and and 105°C (reflux temperature) with a 40/60 (v/v) mixture of hydrochloric acid and glacial acetic acid. It is obvious that the said mild conditions are not restricted to those preferred ones but that they may range from 3 to 20 hours at a temperature of between 90 and 110°C for either mineral acid/glacial acetic acid mixtures (containing at least 10% of mineral acid) or for hydrochloric acid alone.

To avoid possible oxidation of the reaction product, a reducing agent is added to the medium. Convenient reducing agents are sulfur dioxide, which is bubbled through the medium before heating, sodium bisulfite or sodium dithionite.

METHOD II

According to this procedure, the derivatives of general formula I are prepared as described in scheme 6 shown hereinafter. An appropriately substituted benzaldehyde of general formula II is reacted with a stoichiometric amount of N-acetylglycine in the presence of an excess of acetic anhydride. The reaction is carried out in a suitable solvent (such as an alcohol/water mixture) under the influence of heat (reflux), preferably in the presence of sodium acetate, in order to yield the azlactone.

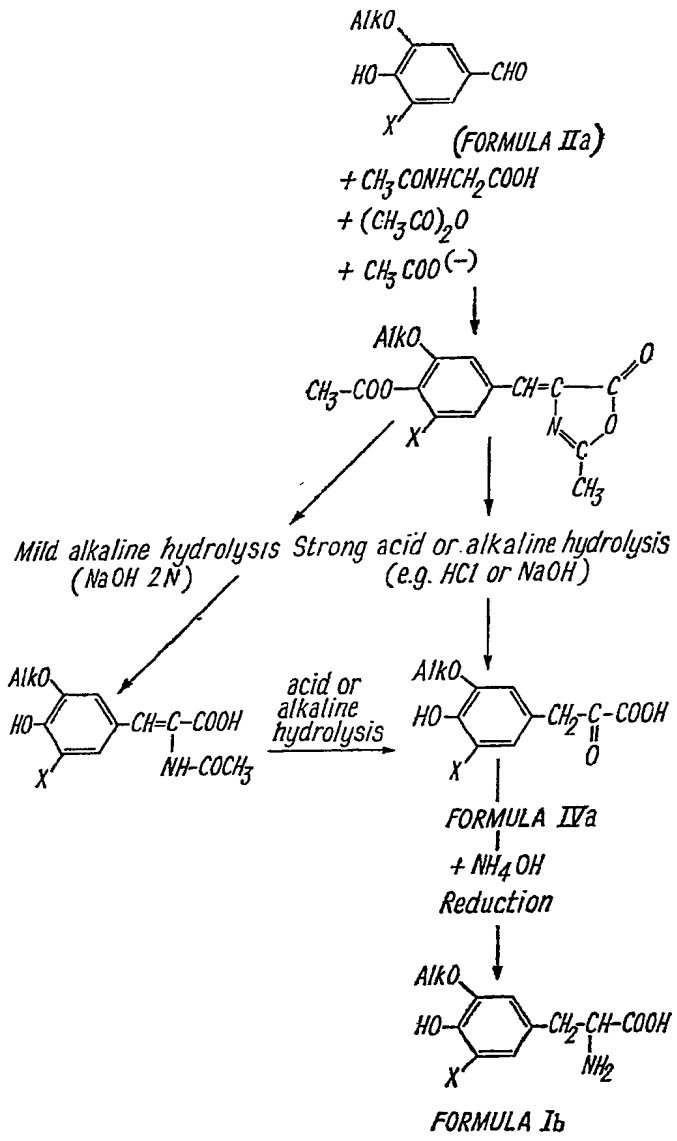
The obtained azlactone is then converted into the corresponding phenyl-pyruvic acid derivative by either strong alkalis or strong acids, alkalis being preferred, the reaction being conducted under the influence of heat in an inert solvent, such as water or a water-alcohol mixture, the concentration of alkali being at least 10%.

Alternatively, using mild alkaline conditions (alkali concentration less than 10%), an intermediate 2-acetamido-3-substituted phenyl-propenoic acid is obtained which is further converted into the corresponding substituted phenyl-pyruvic acid by strong mineral acids or alkalis.

The substituted phenylpyruvic acids of formula IVa (or formula IV) may be converted to the compounds of wherein R_3 and Z are both hydrogen formula I by reduction under mild conditions in ammonium hydroxide solution.

The following scheme 6 illustrates the procedure starting from a 3-alkoxy-4-hydroxy-5-halo-benzaldehyde (formula IIa).

Scheme 6



Owing to the fact that the compounds of general formula have an asymmetrical carbon atom, they may exist as 'D' and 'L' isomers as well as in the optically inactive 'DL' form. At the end of the above reaction schemes, there is obtained the 'DL' form. The 'D' and 'L' isomers are obtained therefrom by optical resolution using procedures well known to the art, for instance by salt-formation with an optically active base or by chromatography on cellulose and elution with a polar solvent (e.g. n-butanol saturated with 3N hydrochloric acid). Both isomers, as well as the optical resolution step, are within the scope of this invention.

The invention is illustrated by the following non-limitative examples.

Words indicated by an asterisk are Registered Trade Marks.

EXAMPLE 1

Vanillin (51 g) is dissolved in 600 ml of glacial acetic acid and a current of chlorine is allowed to pass through the solution until formation of hydrochloric acid is exhausted. The reaction medium is then kept overnight at 40°C and the obtained precipitate is filtered, washed with water and dried over phosphorus pentoxide under reduced pressure to yield 5-chlorovanillin, m.p. 164—165°C.

A 40 g aliquot of the obtained 5-chlorovanillin is treated with 40 ml of a 30% aqueous sodium hydroxide solution and 210 ml of water.

There is added 6.4 g of sodium borohydride and the reaction medium is stirred for 15 hours and then acidified with a 50% aqueous hydrochloric acid solution.

The obtained precipitate is filtered, washed with water and dried over phosphorus pentoxide at 40°C under reduced pressure to yield 5-chloro-vanillic alcohol, m.p. 111.2—112.6°C after recrystallization from water.

A 20 g aliquot of this substituted vanillic alcohol is suspended in 100 ml of anhydrous benzene and a current of dry hydrochloric acid is allowed to pass through the medium until dissolution is completed. The solvent is then evaporated under reduced pressure and the residue is treated twice with 150 ml of anhydrous benzene, which is thereafter evaporated to eliminate residual hydrochloric acid. The residue is dried under reduced pressure at 40°C. In this way, there is obtained 3-methoxy-4-hydroxy-5-chloro-benzyl chloride, m.p. 64.6—66.6°C.

Diethyl acetamidomalonate (32.2 g) is suspended in 50 ml of anhydrous ethanol and an ethanolic solution of sodium ethoxide (2.1 g of sodium in 100 ml of ethanol) is added thereto. The medium is stirred for half an hour at 70°C.

There is then added a solution of 16 g of the above obtained 3-methoxy-4-hydroxy-5-chlorobenzyl chloride in 45 ml of anhydrous ethanol and the medium is refluxed for 17 hours.

The medium is concentrated to one half of its initial volume and the reaction product is precipitated by pouring the medium into water. The precipitate is filtered, washed with water and dried over phosphorus pentoxide at 40°C under reduced pressure to yield diethyl acetamido-(3-methoxy-4-hydroxy-5-chlorobenzyl)-malonate, m.p. 154.2—155.6°C after recrystallization from benzene.

Diethyl acetamido-(3-methoxy-4-hydroxy-5-chlorobenzyl) malonate (8 g) is dissolved in 20 ml of glacial acetic acid at 60—70°C. Sulfur dioxide is bubbled through the solution and 32 ml of concentrated hydrochloric acid is added thereto.

The medium is heated for 9 hours at 95°C and the solvent is then evaporated. The residue is taken up with four portions of water, evaporated to eliminate hydrochloric acid and discoloured with charcoal in water.

The solution is filtered, the solvent is evaporated and the residue is taken up in a small amount of butanol.

The solvent is evaporated and the residue is dissolved in hot butanol from which it is precipitated by addition of anhydrous ether. The precipitate is filtered and dried under reduced pressure at 40°C to yield DL-3-methoxy-4-hydroxy-5-chloro-β-phenylalanine hydrochloride, m.p. 218—220°C (dec.), soluble in water and in ethanol.

EXAMPLE 2

Vanillin (15.2 g) is dissolved in 100 ml of glacial acetic acid and a solution of 16 g of bromine in 100 ml of glacial acetic acid is added dropwise thereto. The precipitate is filtered, washed with water and dried over phosphorus pentoxide under reduced pressure to yield 5-bromovanillin, m.p. 162—164°C.

A 23.1 g aliquot of 5-bromovanillin is suspended in 150 ml of water and dissolved therein by addition of 45 ml of aqueous sodium hydroxide (10%). An aqueous solution of 2.08 g of sodium borohydride is added with stirring within 15 minutes. The yellow colour of the solution slowly disappears and stirring is maintained for 15 hours at room temperature. By addition of aqueous hydrochloric acid (6N) to pH 5, there is obtained a precipitate which is filtered, washed with water until the pH of the washings is 7 and dried over phosphorus pentoxide under reduced pressure to yield 5-bromo-vanillic alcohol, m.p. 133—134°C.

21 g aliquot of 5-bromo-vanillic alcohol is suspended in 150 ml of anhydrous benzene and a current of dry hydrochloric acid is allowed to pass through the medium, which is maintained at a temperature of 7—8°C. The current of hydrochloric acid is still maintained for 15 minutes after complete dissolution of the reactant. The medium is then dried over anhydrous-sodium sulfate and filtered on sintered glass. The filtrate is evaporated to dryness and the residue is treated with two portions of 150 ml of anhydrous benzene which are evaporated to eliminate residual hydrochloric acid. The final residue is again dissolved in a 150 ml portion of anhydrous benzene and the

solution is poured into 1.5 l of hexane previously dried over calcium chloride. The precipitate is filtered and dried to yield 3-methoxy-4-hydroxy-5-bromobenzyl chloride, m.p. 84—86°C.

Diethyl acetamidomalonate (6.95 g) is suspended in 12 ml of anhydrous ethanol and an ethanolic solution of sodium methoxide (0.735 g of sodium in 24 ml of ethanol) is added thereto with stirring. In this way, there is obtained a yellowish solution which is stirred for 30 minutes at 65°C.

There is then added thereto a solution of 4 g of the above obtained 3-methoxy-4-hydroxy-5-bromobenzyl chloride in 15 ml of anhydrous ethanol. A precipitate of sodium chloride appears immediately and the medium is refluxed for 3 1/2 hours and then evaporated to dryness. The residue is then taken up with 500 ml of water. After vigorous stirring, the obtained white precipitate is filtered on sintered glass, washed with water and dried over phosphorus pentoxide at 40°C under reduced pressure to yield diethyl acetamido-(3-methoxy-4-hydroxy-5-bromobenzyl)-malonate, m.p. 161—162°C, purity by phenol-group titration: 96.5%.

Diethyl acetamido-(3-methoxy-4-hydroxy-5-bromobenzyl)-malonate (5 g) is dissolved at 70°C in a mixture of 12 ml of glacial acetic acid and 20 ml of concentrated hydrochloric acid and the solution is saturated with sulfur dioxide.

The medium is then heated for 6 hours at 95°C (reflux).

After that reaction time, the solvent is evaporated.

The residue is taken up with anhydrous ether.

After filtration, the precipitate is dried at 40°C under reduced pressure to yield DL-3-methoxy-4-hydroxy-5-bromo-β-phenylalanine hydrochloride.

Rf = 0.65 (±0.05) and 0.77 (±0.05) by ascending paper chromatography on Whatman* No 1, elution with n-butanol saturated with hydrochloric acid.

Example 3

A solution of 1 g of DL-3-methoxy-4-hydroxy-5-bromo-β-phenylalanine hydrochloride in 50 ml of water is batch treated by 2.5 ml of anionic-ion exchange Amberlite* LA2 (a liquid product from Rohm and Hass Co, Philadelphia, Pa, U.S.A.) in 60 ml of benzene.

The medium is stirred for 24 hours. The aqueous layer is then washed twice with benzene and the organic layer is washed twice with water.

The aqueous portions are collected and the solvent is evaporated to yield DL-3-methoxy-4-hydroxy-5-bromo-β-phenylalanine, free base, purity by acid/base titration: 96.4%.

Example 4

DL-3-methoxy-4-hydroxy-5-bromo-β-phenylalanine hydrochloride (16.33 g) is dissolved in 50 ml of water. By addition of triethylamine in alcohol, the pH value of the solution is brought to 5.1. The solution is filtered and the filtrate is evaporated to dryness. The residue is treated with two portions of ethanol which is evaporated.

The residue is triturated first with two portions of chloroform in order to eliminate the triethylamine hydrochloride and thereafter with acetone. The solution is filtered and the filtrate is evaporated to dryness.

The residue is recrystallized from hot water to yield DL-3-methoxy-4-hydroxy-5-bromo-β-phenylalanine, purity by acid/base titration: 95.2%, water content: 2.4%.

Example 5

A solution of 1 g of DL-3-methoxy-4-hydroxy-5-bromo-β-phenylalanine (hydrochloride) in 25 ml of anhydrous ethanol is saturated at 0°C by gaseous hydrochloric acid. The solution is then heated for one hour at 80°C. The solvent is evaporated and the residue is taken up with two portions of anhydrous ethanol and precipitated by pouring the solution into anhydrous ether to yield DL-3-methoxy-4-hydroxy-5-bromo-β-phenylalanine (hydrochloride)ethyl ester, m.p. 194—197° C., purity and acid/base titration: 100%.

Example 6

To a solution of 1 g of DL-3-methoxy-4-hydroxy-5-bromo-β-phenylalanine (hydrochloride) in 33.6 ml of aqueous sodium hydroxide (N), there is added dropwise with stirring 2.4 ml of acetic anhydride. The reaction is exothermic and the colour of the medium passes from orange to yellow.

The medium is stirred at room temperature for 17 hours and then filtered. The pH value of the filtrate is brought to 2.3 with hydrochloric acid and the solvent is then evaporated by azeotropic distillation. The residue is taken up with methylene chloride. After filtration, the solution is treated with charcoal, filtered, concentrated

to a small volume and hexane is added to yield a precipitate which is filtered and dried under reduced pressure. In this way, there is obtained DL-3-methoxy-4-acetoxy-5-bromo-N-acetyl-β-phenylalanine.

When this product is examined by thin layer chromatography on Kieselgel G (a product from E. Merck, Darmstadt, Germany) in the system propanol/water: 75/25, followed by detection with bromocresol purple, there is obtained one single spot, response to ninhydrin and ferric chloride being negative.

EXAMPLE 7

To a solution of 50 g of DL-3-methoxy-4-hydroxy-5-bromo-β-phenylalanine (hydrochloride) in 500 ml of aqueous sodium hydroxide (N), there is added 0.5 g of sodium hydrosulfite and, slowly, acetic anhydride to pH 7; the addition of acetic anhydride is then continued while maintaining the pH value at about 8 with aqueous sodium hydroxide (N).

After complete addition of the acetic anhydride reactant (36.25 ml), the pH is brought to 10.8 with aqueous sodium hydroxide (of which the total amount employed is 602.5 ml). The temperature is maintained between 30 and 40°C during the whole reaction time.

The medium is kept for four hours at room temperature and then acidified with hydrochloric acid (6N). Crystallization of the N-acetylated compound begins at a pH value of about 4 but acidification is continued to pH 1.4 and crystallization is allowed to take place at that pH for 15 hours at 4°C.

The obtained precipitate is then filtered, washed with cold water and dried over phosphorus pentoxide under reduced pressure at 50°C to yield DL-3-methoxy-4-hydroxy-5-bromo-N-acetyl-β-phenylalanine, m.p. 222—223°C (dec.).

When this product is examined by thin layer chromatography on Kieselgel G (a product from E. Merck, Darmstadt, Germany) in the system propanol/water: 75/25, followed by detection with either bromocresol purple or ferric chloride, there is obtained one single spot, the response to ninhydrin being negative.

EXAMPLE 8

To 31.6 ml of an ethanolic solution (4.3M) of L(−) ephedrine diluted with 84.5 ml of acetone, there is added 45 g of DL-3-methoxy-4-hydroxy-5-bromo-N-acetyl-β-phenylalanine.

After further addition of 90 ml of acetone, a solution is obtained by heating with stirring. The solution is kept for five days at room temperature.

The obtained crystals are then filtered, washed with acetone, dried, powdered and taken up with 400 ml of acetone. The suspension is stirred for one hour and then filtered.

The collected crystals are dissolved with stirring in 80 ml of hot anhydrous ethanol. By slow addition of 360 ml of ether with stirring and with cooling there is obtained a precipitate which is allowed to stand for four hours at room temperature before being filtered, washed with ether and dried under reduced pressure.

In this way, there is obtained the L(−)ephedrine salt of (−)3-methoxy-4-hydroxy-5-bromo-N-acetyl-β-phenylalanine, $[\alpha]_D^{25} = -66°$ (c = 1 in ethanol), m.p. 128—131°C.

EXAMPLE 9

In 1075 ml of a water/ethanol 25/75 mixture, there is dissolved 21.5 g of L(−) ephedrine salt of (−)3-methoxy-4-hydroxy-5-bromo-N-acetyl-β-phenylalanine.

The solution is poured on to a 5 cm diameter column of Amberlite* IR 124 (a product of Rohm & Haas, Philadelphia, Pa, U.S.A.) under acid form, the flow rate being adjusted to 5 ml/minute.

Elution is performed with a water/ethanol 25/75 mixture.

The eluate is concentrated to a small volume and then taken up with ethanol, treated with charcoal and filtered.

The solvent is evaporated under reduced pressure at 40°C to yield (−)3-methoxy-4-hydroxy-5-bromo-N-acetyl-β-phenylalanine, $[\alpha]_D^{25} = -40°$ (c = 1 in ethanol).

EXAMPLE 10

A suspension of 11.5 g of (−)3-methoxy-4-hydroxy-5-bromo-N-acetyl-β-phenylalanine in 230 ml of hydrochloric acid (1.2N) is saturated with sulfur dioxide. A solution is obtained after heating for 30 minutes with stirring at 110°C (bath temperature) but heating and stirring are maintained for a further period of 3½ hours in order to perform complete hydrolysis.

After that reaction time, the solution is discoloured with charcoal and filtered. The solution is concentrated to a small volume, taken up with water and evaporated

to dryness by azeotropic distillation. The residue is taken up with anhydrous ether. After filtration and drying under reduced pressure at 40°C there is obtained (+)3-methoxy-4-hydroxy-5-bromo-β-phenylalanine (hydrochloride) $[\alpha]_D^{25} = +10°$ (c=1 in water).

EXAMPLE 11

DL-3-methoxy-4-hydroxy-5-bromo-β-phenylalanine hydrochloride (15 g), as obtained at the end of example 2, is dissolved in 100 ml of aqueous sodium hydroxide (N).

There is added thereto dropwise and with stirring 15 ml of palmitoyl chloride dissolved in 30 ml of freshly distilled tetrahydrofuran, the pH of the medium being adjusted between 6.5 and 7.5 with aqueous sodium hydroxide (N) during the addition. When the addition is completed, the pH is brought to 8. During the next period of 5 hours, the stirring is maintained and the pH value of the medium is slowly brought to 9 by addition of aqueous sodium hydroxide (N), and the medium is then allowed to stand overnight.

The solution is concentrated under reduced pressure in the presence of a small amount of sodium dithionite to 1/3 of its initial volume and extracted with two portions of ether, the pH value being brought to 2 by addition of hydrochloric acid (N).

The organic layers are collected, discoloured with charcoal, filtered, dried over anhydrous sodium sulfate and concentrated under reduced pressure. By addition of hexane there is obtained a precipitate which is filtered on sintered glass and dried under reduced pressure at 40°C to yield 3-methoxy-4-hydroxy-5-bromo-N-palmitoyl-β-phenylalanine, m.p. 104—107°C.

EXAMPLE 12

Diethyl acetamidomalonate (38.43 g) is dissolved in 300 ml of freshly distilled dimethylformamide and 8.17 g of 50% sodium hydride is added thereto.

The medium is stirred for one hour at 25°C and there is then added thereto 39.43 g of 3,4-dimethoxy-5-bromobenzyl chloride (PSCHORR, Liebig's Annalen *391*, 29—33, 1912) dissolved in 200 ml of dimethylformamide. After heating for 4 hours at 105°C, the yellowish solution is poured into 3 liters of water. The obtained precipitate is filtered, washed with water and dried over phosphorus pentoxide at 70°C to yield diethyl acetamido-(3,4-dimethoxy-5-bromo-benzyl)-malonate, m.p. 118—119.5°C.

Diethyl acetamido-(3,4-dimethoxy-5-bromobenzyl)-malonate (10 g) is dissolved in a mixture of 60 ml of glacial acetic acid and 60 ml of concentrated hydrochloric acid and the solution is saturated with sulfur dioxide.

The medium is then heated for 20 hours at 95°C (reflux).

After that reaction time, the solvent is evaporated and the residue is taken up with 100 ml of water, and discoloured with charcoal. The pH of the solution is brought to 1.5 by addition of aqueous sodium hydroxide (20%) to precipitate DL-3,4-dimethoxy-5-bromo-β-phenylalanine which is filtered, washed with water and taken up with hot hydrochloric acid (6N).

The obtained precipitate is filtered, washed with iced water and dried under reduced pressure to yield DL-3,4-dimethoxy-5-bromo-β-phenylalanine (hydrochloride), purity 99% (by titrimetry of the amino group), Rf=0.53 (±0.05) by thin layer chromatography on Silicagel G (a product from E. Merck, Darmstadt, Germany), elution with ethanol/ammonium hydroxide (25%): 80/20.

EXAMPLE 13

A mixture of 5-bromovanillin (115 g), N-acetylglycine (58.5 g), sodium acetate (82 g) and acetic anhydride (150 ml) is heated to 110°C for two hours.

There is then added 1.25 l of a 1/1 mixture of ethanol/water and the reaction medium is stirred for 30 minutes, filtered, washed with another 500 ml portion of the ethanol/water mixture and dried at 40°C under reduced pressure to yield 130 g of an azlactone.

A 50 g aliquot of the obtained azlactone is dissolved in 500 ml of aqueous sodium hydroxide (2N) and the solution is heated for two hours at 60—70°C. The pH of the solution is then brought to 5.5 with hydrochloric acid (6N) and the solution is discoloured with charcoal. After filtration, the pH of the solution is brought to 2 with hydrochloric acid (6N).

The obtained crystals are filtered, washed with water and dried under reduced pressure to yield 49 g of 2-acetylamino-3-(3'-methoxy-4'-hydroxy-5'-bromo-phenyl)-propenoic acid.

A 25 g aliquot of this substituted propenoic acid is suspended in 200 ml of a glacial acetic acid/hydrochloric acid (12N) mixture (30/70) and heated for six hours

at the reflux temperature with vigorous stirring. The medium is then cooled and poured with stirring into two liters of water.

The obtained crystals are filtered, washed with water and dried under reduced pressure at 40°C to yield 17.9 g of 3-methoxy-4-hydroxy-5-bromophenylpyruvic acid, m.p. 238—240°C (dec.), Rf = 0.25 (±0.05) by thin layer chromatography on Silica-gel G (a product from E. Merck, Darmstadt, Germany), elution with benzene/methanol/acetic acid: 45/8/4, followed by detection with ferric chloride.

A 10 g aliquot of the obtained acid is dissolved in 100 ml of concentrated ammonium hydroxide and a solution of 350 mg of sodium borohydride in 10 ml of water is added thereto with stirring. Stirring is maintained for two hours. After that reaction time, excess ammonium hydroxide is eliminated by evaporation of the solvent under reduced pressure.

The residue is taken up with water which is thereafter evaporated and the residue is again taken up with water.

The obtained solution is acidified with concentrated hydrochloric acid to pH 1.5.

The solution is stirred for one hour and the solvent is then evaporated, taken up with two successive portions of water and then with n-butanol and the solvent is evaporated. The residue is taken up with ethanol. The insoluble fraction (mineral salts) is eliminated by filtration and the filtrate is concentrated to give a syrup. By addition of ether, there is obtained DL-3-methoxy-4-hydroxy-5-bromo-β-phenylalanine hydrochloride with the same characteristics as those of the product obtained at the end of example 2.

EXAMPLE 14

To a mixture of 3-ethoxy-4-hydroxy-benzaldehyde (49.86 g) and sodium acetate (24.6 g) in 300 ml of glacial acetic acid, there is added dropwise a solution of 48 g of bromine in 300 ml of glacial acetic acid. The medium is stirred for four hours at room temperature and then poured into water saturated with sulfur dioxide. The precipitate is washed with water and dried under reduced pressure to yield 3-ethoxy-4-hydroxy-5-bromo-benzaldehyde (m.p. 142°C).

A 65 g aliquot of the obtained substituted benzaldehyde is poured into 500 ml of water and dissolved therein by addition of 273 ml of aqueous normal sodium hydroxide.

Sodium borohydride (6 g) is added with stirring within 15 minutes and stirring is maintained for 48 hours at room temperature. By addition of aqueous hydrochloric acid (6N) to pH 2.5), there is obtained a precipitate which is filtered, washed with water to neutral pH of the washings and dried at 40°C under reduced pressure to yield 3-ethoxy-4-hydroxy-5-bromobenzyl alcohol, m.p. 130—131°C.

A 20 g aliquot of this alcohol is suspended in 300 ml of anhydrous benzene and a current of dry hydrochloric acid is allowed to pass through the medium for three hours.

The medium is then filtered on sintered glass and the filtrate is evaporated to dryness to yield 3-ethoxy-4-hydroxy-5-bromobenzyl chloride.

Diethyl acetamidomalonate (17.5 g) is suspended in 100 ml of dimethyl formamide and 4.1 g of a 50% (w/w) suspension of sodium hydride in oil is added thereto with stirring. In this way, there is obtained a solution which is stirred for 30 minutes, the temperature then reaching 90°C.

There is then added a solution of 19.5 g of the above obtained 3-ethoxy-4-hydroxy-5-bromobenzyl chloride in 150 ml of dimethyl formamide and the temperature of the medium is maintained at 100°C for five hours.

The reaction medium is then poured into water to yield a precipitate which is filtered on sintered glass, washed with water and dried over phosphorus pentoxide at 40°C under reduced pressure to yield diethyl acetamido-(3-ethoxy-4-hydroxy-5-bromobenzyl)-malonate, m.p. 154—156°C, purity by phenol-group titration: 99%.

The obtained diethyl acetamido-(3-ethoxy-4-hydroxy-5-bromobenzyl)-malonate is then poured into a mixture of 200 ml of glacial acetic acid and 200 ml of hydrochloric acid (6N) and the medium is heated for 6 hours at 95°C (reflux).

After that reaction time, the solvent is evaporated.

The residue is taken up with water and the solution is discoloured with charcoal and filtered. The obtained yellow solution is evaporated to dryness and the residue is dried at 40°C under reduced pressure to yield DL-3-ethoxy-4-hydroxy-5-bromo-β-phenylalanine hydrochloride, (purity 99% by titrimetry of the amino group).

EXAMPLE 15

A solution of vanillin (500 g), sodium bicarbonate (250 g) and postassium iodide

(747 g) in 10 l of water is treated with 834 g of iodine. The medium is stirred for four hours and kept overnight. The obtained crystals are treated with an aqueous solution (10%) of sodium thiosulfate, filtered, washed with water and dried under reduced pressure to yield 5-iodovanillin.

A 27.8 g aliquot of the above obtained 5-iodovanillin, 11.7 g of N-acetylglycine, 8.2 g of sodium acetate and 30.6 g of acetic anhydride are heated to 105°C for four hours. The reaction medium is taken up with 125 ml of a 1/1 mixture of ethanol and water and the crystals are filtered and dried under reduced pressure.

The obtained azlactone is recrystallized from acetic acid (m.p. 194—195°C) and dissolved in 300 ml of aqueous sodium hydroxide (stirring for one hour at 55°C).

The solution is acidified to pH 5.3 with hydrochloric acid (6N), discoloured with charcoal, filtered and the pH is brought to 1.5 with another portion of hydrochloric acid (6N). The solution is then heated with stirring at 55°C until crystallization occurs.

The crystals are filtered, washed with water and dried under reduced pressure to yield 2-acetamido-3-(3'-methoxy-4'-hydroxy-5'-iodo-phenyl)-propenoic acid, m.p. 218.5—220°C.

This acid is suspended in 100 ml of an acetic acid/hydrochloric acid (12N) mixture (30/70) and the medium is heated for three hours at 90°C with stirring.

After that reaction time, the precipitate is filtered, washed with water and dried under reduced pressure to yield 3-methoxy-4-hydroxy-5-iodo-phenylpyruvic acid m.p. 226—229°C, Rf = 0.22 (±0.05) by thin layer chromatography on Silicagel G (a product from E. Merck, Darmstadt, Germany) in the system benzene/methanol/acetic acid: 45/8/4.

This acid is dissolved in 50 ml of concentrated ammonium hydroxide and the solution is stirred for 15 minutes. There is then added 0.250 g of sodium borohydride and the medium is stirred for two hours.

After that reaction time, the pH of the solution is brought to 1.2 with hydrochloric acid (6N) and the solvent is evaporated under reduced pressure. The residue is taken up with three successive portions of water in order to eliminate the free hydrochloric acid.

This residue is then taken up with n-butanol, the solvent is evaporated and the residue is taken up with a minimum of hot n-butanol and treated with anhydrous ether.

The crystals are filtered, washed with anhydrous ether and dried under reduced pressure to yield DL-3-methoxy-4-hydroxy-5-iodo-β-phenylalanine (hydrochloride) m.p. 187—190°C, Rf = 0.35 (±0.05) by thin layer chromatography in the system methanol/chloroform/ammonium hydroxide: 20/20/5.

Example 16

5-Bromovanillin (231 g) and anhydrous aluminium chloride (146.7 g) are suspended in one liter of methylene chloride and anhydrous pyridine (348 g) is added dropwise thereto. The medium is heated for 24 hours at 45°C and then poured into two liters of hydrochloric acid (4N) at 0°C. The precipitate is filtered, washed with water and dried under reduced pressure to yield 5-bromo-protocatechualdehyde (m.p. 228—229°C after recrystallization from ethanol).

A 108.5 g aliquot of 5-bromo-protocatechualdehyde, 43.3 g of sodium bicarbonate, 100 ml of methyl iodode and 700 ml of acetone (dried over potassium carbonate) are refluxed for 20 hours.

The solution is then evaporated to dryness and the residue is taken up in chloroform. The obtained solution is treated with dry hydrochloric acid. The medium is filtered and the solution is poured onto 200 g of Silicagel 7729 (a product from E. Merck, Darmstadt, Germany), discoloured on charcoal and concentrated up to crystallization occurs. After filtration, there is obtained 5-bromoisovanillin (m.p. 116.5—117.5°C).

A 32.4 g aliquot of 5-bromoisovanillin, 16.4 g of N-acetylglycine, 22.9 g of sodium acetate and 27 ml of acetic anhydride are heated for two hours at 110°C. The reaction medium is poured into 800 ml of water. The obtained precipitate is filtered, washed with water and dried under reduced pressure at 40°C over phosphorus pentoxide.

After recrystallization from glacial acetic acid, filtration, washing with ethyl ether and drying, there is obtained an azlactone, m.p. 210—211°C, Rf = 0.66 (±0.05) by thin layer chromatography on Silicagel G (a product of E. Merck, Darmstadt, Germany) in the system benzene/dioxane/acetic acid: 90/25/4.

A 20 g aliquot of the obtained azlactone is dissolved in 250 ml of aqueous sodium hydroxide (2N) and heated for one hour at 70°C with stirring.

The pH of the solution is then brought to 1.5 with hydrochloric acid (6N) and the reaction medium is heated for one hour at 70°C. The obtained crystals are filtered, washed with water and dried at 40°C under reduced pressure to yield 2-acetamido-3-(3'-hydroxy-4'-methoxy-5'-bromo-phenyl)-propenoic acid, m.p. 218—219°C, Rf = 0.25 (±0.05) by thin layer chromatography on Silicagel G (a product from E. Merck, Darmstadt, Germany) in the system benzene/methanol/acetic acid: 45/8/4, followed by detection with ferric chloride.

A 12 g aliquot of the obtained 2-acetamido-3-(3'-hydroxy-4'-methoxy-5'-bromo-phenyl)-propenoic acid in a mixture of 30 ml of acetic acid and 70 ml of hydrochloric acid (12N) is heated for 5 hours at 95°C.

The hot medium is then filtered on charcoal and crystallization occurs by cooling of the solution.

After filtration, the crystals are washed with water and dried at 40°C under reduced pressure to yield 3-hydroxy-4-methoxy-5-bromo-phenylpyruvic acid, m.p. 203—205°C, Rf = 0.23 (±0.05) by thin layer chromatography in the system benzene/methanol/acetic acid: 45/8/4, followed by detection with ferric chloride.

A 5 g aliquot of the obtained substituted phenylpyruvic acid is dissolved in 50 ml of concentrated ammonium hydroxide and the solution is stirred for 1/4 hour. There is then added 0.5 g of sodium borohydride and the medium is stirred for four hours.

The pH of the solution is then brought to 1.5 with hydrochloric acid (6N) and the solvent is evaporated. The residue is taken up with several portions of water, followed by evaporation to eliminate free hydrochloric acid.

The residue is taken up by two portions of butanol, which is thereafter evaporated, and then with a minimum of hot butanol from which crystallization occurs by cooling.

After filtration, washing with ether and drying under reduced pressure, there is obtained DL-3-hydroxy-4-methoxy-5-bromo-β-phenylalanine (hydrochloride), m.p. 151—153°C, Rf = 0.53 (±0.05) by thin layer chromatography on Silicagel G (a product from E. Merck, Darmstadt, Germany) in the system methanol/chloroform/ammonium hydroxide: 20/20/5, followed by detection with ferric chloride.

EXAMPLE 17

DL-3-methoxy-4-hydroxy-5-chloro-β-phenylalanine hydrochloride (4.5 g), as obtained in example 1, is suspended in 150 ml of water and treated with 400 ml of a buffer solution at pH 7.4 (a solution of 23.9 g of disodium phosphate (12 aq) in one liter of water adjusted to pH 7.4 by addition of monopotassium phosphate).

The pH of the solution (6.5) is adjusted to 7.4 by addition of disodium phosphate and, after filtration, there is added 100 ml of the above defined buffer solution and 0.15 g of L-aminoacid oxidase (a product from CALBIOCHEM, Los Angeles, California, U.S.A.). The medium is maintained with stirring at 37°C for 43 hours.

After that reaction time, the pH of the medium is brought to 1.65 by addition of hydrochloric acid (6N), discolouring charcoal is added and the medium is heated to 50°C for 1/2 hour and then filtered. The filtrate is treated with Amberlite LA—2 (a product from Rohm and Haas Co Philadelphia, Pa, U.S.A.) diluted with benzene.

The aqueous layer is separated, washed with benzene, acidified with hydrochloric acid (6N) and the solvent is evaporated. The residue is dissolved in hot ethanol, the solution (after filtration) is concentrated by evaporation, treated with water to eliminate ethanol, extracted with ethyl ether and discoloured with charcoal.

After filtration, the solution is alkalinized and the solvent is evaporated.

The residue is taken up in methanol. After filtration, the solvent is evaporated and the residue is suspended in ethanol, filtered, washed with ethanol and with ether, suspended in a minimum of water and treated with 20 ml of hydrochloric acid (N).

The obtained solution is discoloured, the solvent is evaporated and the residue is taken up in a minimum of ethanol, diluted with ether and the solution is poured into anhydrous ethyl ether to yield a precipitate which is washed with anhydrous ether and dried under reduced pressure at 50°C to yield D(+)3-methoxy-4-hydroxy-5-chloro-β-phenylalanine (hydrochloride). After recrystallization from n-propanol, $[\alpha]_D^{25}$ = between +8.6 and +9.25° (c = 1 in water), Rf = 0.42 (±0.05) by thin layer chromatography on Whatman* cellulose, CC 31 in n-butanol saturated with hydrochloric acid (3N), followed by detection with ninhydrin.

EXAMPLE 18

Ingredients	mg/capsule
3-hydroxy-4-methoxy-5-bromo-β-phenylalanine (hydrochloride)	500
magnesium stearate	20

The above ingredients are thoroughly mixed and passed through an ASTM N° 50 screen into a N° 0 hard gelatin capsule, the volume being if desired adjusted with lactose or another classical inert ingredient well known to the art.

From about one to about four of these capsules are administered by the oral route to hypertensive persons, preferably in two fractions on the same day.

It is understood that this treatment, such as the duration of the treatment, may fluctuate from one case to another according to the hypertensive state and individual reaction of the patient.

EXAMPLE 19

Ingredients	mg/tablet
3-methoxy-4-hydroxy-5-chloro-β-phenylalanine (hydrochloride)	500
starch	150
talc	20
magnesium stearate	5

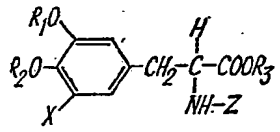
The 3-methoxy-4-hydroxy-5-chloro-β-phenylalanine (hydrochloride), starch, one half of the amount of talc and one half of the amount of magnesium stearate are thoroughly mixed.

The mixture is compressed into tablets which are then ground through an ASTM N° 24 mesh screen. The granules are then thoroughly mixed with the remaining talc and magnesium stearate and the mixture is compressed into tablets.

The tablets are administered by the oral route, the dosage being as defined for the capsules in example 18.

WHAT WE CLAIM IS:—

1. DL-, D- and L- beta-phenylalanine derivatives of the general formula



wherein:
R_1 and R_2 are identical or different and represent methyl or ethyl, one of them being also possibly hydrogen or a carboxylic acid acyl radical of from 2 to 30 carbon atoms,
R_3 represents hydrogen, a pharmaceutically acceptable non-toxic alkali metal, ammonium, a pharmaceutically acceptable non-toxic protonated amine with which the rest of the molecule forms an acid addition salt, an alkyl radical containing from 1 to 30 carbon atoms or an alkenyl radical containing from 2 to 30 carbon atoms, said alkyl or alkenyl radicals having a straight or a branched chain,
X represents chloro, bromo, iodo or fluoro and
Z represents hydrogen or a carboxylic acyl radical of from 2 to 30 carbon atoms,
and their non-toxic acid addition salts.

2. DL-, D- and L- beta-phenylalanine derivatives and the non-toxic acid addition salts thereof according to claim 1
wherein
R_1 and R_2 are different, one of them representing methyl and the other representing hydrogen,
R_3 represents hydrogen,
X represents chloro or bromo and
Z represents hydrogen.

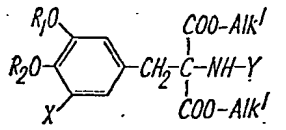
3. DL-, D- and L- 3-methoxy-4-hydroxy-5-bromo-β-phenylalanine and non-toxic acid addition salts thereof.

4. DL-, D- and L- 3-methoxy-4-hydroxy-5-chloro-β-phenylalanine and non-toxic acid addition salts thereof

5. DL-, D- and L- 3-hydroxy-4-methoxy-5-bromo-β-phenylalanine and non-toxic acid addition salts thereof

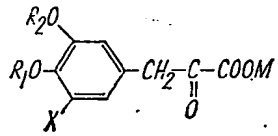
6. DL-, D- and L- 3-hydroxy-4-methoxy-5-chloro-β-phenylalanine and non-toxic acid addition salts thereof

7. A method for the production of those compounds according to claim 1 wherein R_3 and Z are both hydrogen which comprises hydrolysing and decarboxylating substituted 2-benzyl-2-amino-malonic acid esters of the general formula:



wherein R_1, R_2 and X have the same significance as in the formula set out in claim 1, Alk^1 represents a lower alkyl radical with a straight or a branched chain containing from 1 to 4 carbon atoms, and Y represents a formyl, acetyl, benzoyl, phthaloyl or benzyloxy-carbonyl radical, the reaction being conducted in a solvent under the influence of heat in acid medium and in the presence of a reducing agent.

8. A method for the production of those compounds according to claim 1 wherein R_3 and Z are both hydrogen which comprises reducing a substituted phenyl-pyruvic acid of the general formula:



wherein R_1, R_2 and X have the same significance as in the formula set out in claim 1, and M represents hydrogen, a pharmaceutically acceptable non-toxic alkali metal, ammonium or a pharmaceutically acceptable non-toxic protonated amine with which the rest of the molecule forms an acid addition salt, the reaction being carried out under mild conditions in ammonium hydroxide solution.

9. Pharmaceutical preparations comprising as active ingredient at least one beta-phenylalanine derivative according to any one of claims 1 to 6, in association with a pharmaceutically acceptable diluent or carrier.

10. Beta-phenylalanine derivatives according to claim 1 substantially as hereinabove described in the examples.

11. Process for producing phenylalanine derivatives according to claim 1, substantially as hereinabove described in the examples.

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Agent for the Applicants.

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